PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004274	08.10.2004	09.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K35/74, A61K39/095

Applicant
HEALTH PROTECTION AGENCY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/004274

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22 (completely), 23-26,31,33-36 (all partially)

because:

☒ the said international application, or the said claims Nos. 23-26,31,33-35 (concerning industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 22 (completely), 36 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/004274

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-12,23,24,26,31-36 (all partially), 13-21,25,27-30,37-43 (all completely)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	26
	No:	Claims	1-21,23-25,27-43
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21,23-43
Industrial applicability (IA)	Yes:	Claims	1-21,27-30,32,36-43
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/004274

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/004274

The present application describes an outer membrane vesicle-based vaccine against *Neisseria* that is Opa-free or contains Opa which is unable to bind to CEACAM1, and antagonists of Opa/CEACAM1 interaction.

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: PEETERS C C A M et al. Phase I clinical trial with a hexavalent PorA containing meningococcal outer membrane vesicle vaccine. VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, 1996, vol. 14, pages 1009-1015

D2: Boulton I C et al. Neisserial binding to CEACAM1 arrests the activation and proliferation of CD4+ T lymphocytes. Nature immunology, 2002, vol. 3, pages:229 - 236

D3: Cohen M S et al. Human experimentation with *Neisseria gonorrhoeae*: progress and goals. The Journal of infectious diseases, 1999, vol. 179 Suppl 2 , pages S375 - S379

D4: NORMARK STAFFAN ET AL: "Gonococci cause immunosuppression by engaging a coinhibitory receptor on T lymphocytes." NATURE IMMUNOLOGY. MAR 2002, vol. 3, no. 3, pages 210-211

D5: DEHIO C ET AL: "The role of neisserial Opa proteins in interactions with host cells." TRENDS IN MICROBIOLOGY, vol. 6, no. 12, December 1998, pages 489-495

D6: GRANT C C ET AL: "Proteoglycan receptor binding by *Neisseria gonorrhoeae* MS11 is determined by the HV-1 region of OpaA." MOLECULAR MICROBIOLOGY, vol. 32, no. 2, April 1999, pages 233-242

D7: VAN PUTTEN J P ET AL: "Binding of syndecan-like cell surface proteoglycan receptors is required for *Neisseria gonorrhoeae* entry into human mucosal cells." THE EMBO JOURNAL, vol. 14, no. 10, 15 May 1995, pages 2144-2154

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Regarding Invention I:

Claims 23,24,26,31,33-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Regarding Invention II:

Claims 23-26,31,33-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV
Lack of unity of invention

This Authority considers that there are 3 inventions covered by the claims indicated as follows:

I: **Claims 1-12,23,24,26,31-36 (all partially), 13-17 (all completely)** directed to a method of selecting or preparing microorganisms, compositions or vaccines that are free of OPA for treatment.

II: **Claims 1-12,23,24,26,31-36 (all partially), 18-21,25,27-30,37-43 (all completely)** directed to a method of selecting or preparing microorganisms, compositions or vaccines that contain OPA which does not bind to CEACAM1 for treatment.

III: **Claims 22 (completely), 36 (partially)** directed to a composition comprising *Neisseria* outer membrane vesicles which comprise an antagonist which inhibits binding of Opa to CEACAM1.

The reasons for which the inventions do not meet the requirements of unity of invention as defined in Rule 13.1 PCT, are as follows:

1 The concept underlying the present application is that avoidance of Opa/CEACAM1 interaction increases the immunogenicity of a meningococcal vaccine.

The latter concept, however, has been disclosed already by document D2, which discloses that the interaction between Opa and CEACAM1 has an immunosuppressive effect on $CD4^+$ T lymphocytes (the whole document) while Opa-negative organisms have not (Fig. 3). Document D2 also discloses to extend the findings of the in vitro studies to in vivo studies (page 234, right-hand column, paragraph 3), and cites in this context D3, which discloses human experimentation with *Neisseria gonorrhoeae* for vaccine testing (the whole document).

Document D4, which is a commentary about D2, also stresses the point to compare the immune response caused by CEACAM1-binding bacteria to that caused by gonococci that do not bind CEACAM1 (the whole document, in particular page 211, right-hand column, last paragraph).

2 In the light of the prior art, it can be concluded that the inventions listed above are not so linked by common inventive concept (Rule 13.1 PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Regarding Invention I:

3 In the light of the disclosure of D1, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17,31,32,36 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this document): meningococcal outer membrane vesicle vaccine, the purity of which is improved by deleting Opa expression (the whole document, e.g. page 1014, right-hand column, paragraph 1) and carrier (page 1010, left-hand column, paragraphs 1-2). Thus, D1 embraces the subject-matter of claims 1-17,31,32,36.

D1 also discloses a vaccine that induces antibacterial IgG antibodies (e.g. Fig. 1). The production of IgG in a host requires isotype switching, which is triggered upon activation of CD4+ T cells. Thus, the vaccine disclosed in D1 may be considered as being free of protein that suppresses activation or proliferation of CD4+ T cells and, thus, embraces the subject-matter of claims 5-8.

The preparation of OMV as described in D1 (page 1010, left-hand column, paragraph 2) is generally carried out at a number of starting bacteria that is higher than 1000. Therefore, D1 also embraces the subject-matter of claim 12.

4 In the light of the disclosure of D2 (see above), the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12,23,24,31-36 is not new in the sense of Article 33(2) PCT.

4.1 Claim 26 meets the requirements of Article 33(2) PCT because its subject-matter was not disclosed in the available prior art.

4.2 Dependent claim 26 does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT), the reasons being as follows: the use of an outer membrane vesicle from a bacterium as vaccine would be a normal option for the person skilled in the art (e.g. D1).

5 The subject-matter of claims 1-16,32,36 is susceptible of industrial application (Article 33(4) PCT).

6 For the assessment of the present claims 23,24,26,31,33-35 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Regarding Invention II:

7 In the light of the disclosure of D1, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12,31,32,36 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this document): meningococcal outer membrane vesicle vaccine, the purity of which is improved by deleting Opa expression (the whole document, e.g. page 1014, right-hand column, paragraph 1) and carrier (page 1010, left-hand column, paragraphs 1-2). Thus, D1 embraces the subject-matter of claims 1-12,31,32,36.

D1 also discloses a vaccine that induces antibacterial IgG antibodies (e.g. Fig. 1). The production of IgG in a host requires isotype switching, which is triggered upon activation of CD4+ T cells. Thus, the vaccine disclosed in D1 may be considered as being free of protein that suppresses activation or proliferation of CD4+ T cells and, thus, embraces the subject-matter of claims 5-8.

The preparation of OMV as described in D1 (page 1010, left-hand column, paragraph 2) is generally carried out at a number of starting bacteria that is higher than 1000. Therefore, D1 also embraces the subject-matter of claim 12.

8 In the light of the disclosure of D2 (see above), the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12,23-25,31-36 is not new in the sense of Article 33(2) PCT.

9 In the light of the disclosure of D7, the present application does not meet the criteria of

Article 33(1) PCT, because the subject-matter of claims 18-21,27-30,39-43 is not new in the sense of Article 33(2) PCT.

Document D7 discloses (the references in parentheses applying to this document): *Neisseria gonorrhoeae* strain MS11 recombinants that produce Opa_{30} or Opa_{50} (page 2151, right-hand column, paragraph 4; Fig. 8), OMV (page 2153, left-hand column, last paragraph), Opa-specific antibody 4B12/C11 (page 2153, right-hand column, first paragraph).

Concerning the subject-matter of claims 39,41 it should be mentioned that a product is not rendered novel by the fact that it is produced by a potentially new process (PCT Guidelines Appendix A5.26[1], 2004).

Note: Opa_{30} and Opa_{50} do not bind CD66a (e.g. D5: Table 1).

10 In the light of the disclosure of D6, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 37,38 is not new in the sense of Article 33(2) PCT.

Document D6 discloses (the references in parentheses applying to this document): mutated OpaA, mAb 4B12 (Fig. 2, 4; pages 239-240).

10.1 Claim 26 meets the requirements of Article 33(2) PCT because its subject-matter was not disclosed in the available prior art.

10.2 Dependent claim 26 does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT), the reasons being as follows: the use of an outer membrane vesicle from a bacterium as vaccine would be a normal option for the person skilled in the art (e.g. D1).

11 The subject-matter of claims 1-12,18-21,27-30,32,36-43 is susceptible of industrial application (Article 33(4) PCT).

12 For the assessment of the present claim 23-26,31,33-35 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004014417 A	19 Feb 2004	31 July 2003	5 March 2003

Re Item VIII
Certain observations on the international application

Regarding Invention I:

13 The application does not meet the requirements of Article 6 PCT, because claim 35 is not clear. It is not clear what weight% of Opa the predetermined level has.

14 The application does not meet the requirements of Article 6 PCT, because claim 36 is not clear. It is not clear in comparison to which medicament and to which extent the immune stimulation is enhanced by the medicament of claim 36.

15 The expression "incorporated herein" on page 10, line 1 should have been deleted from the description. If matter in the documents referred to is essential to satisfy requirements of Art. 5 PCT, then this matter should be expressly incorporated into the description.

16 The term "substantially" used in claims 1,2,5-7,9,12,13,36 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

Regarding Invention II:

17 Claims 21,27,29 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, i.e. as mimic, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

18 The application does not meet the requirements of Article 6 PCT, because claim 35 is not clear. It is not clear what weight% of Opa the predetermined level has.

19 The application does not meet the requirements of Article 6 PCT, because claim 36 is not clear. It is not clear in comparison to which medicament and to which extent the immune stimulation is enhanced by the medicament of claim 36.

20 The subject-matter of claims 39,41 is defined in the term of process for its preparation ('product-by-process' claims).
Claims for products, defined in terms of a process of manufacture, are considered as meeting the requirements of Article 6 PCT provided there is no other information available in the application, which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter. In consequence, the conditions to define a product by its process of production are that there are no other parameters available for a further definition of the product, which is not the case here.

21 In order to avoid any ambiguity with regard to Rule 67.1(iv) PCT, it should have been stated that subject-matter of claim 43 is performed in vitro or on isolated cells.

22 The expression "incorporated herein" on page 10, line 1 should have been deleted from the description. If matter in the documents referred to is essential to satisfy requirements of Art. 5 PCT, then this matter should have been expressly incorporated into the description.

23 The term "substantially" used in claims 1,2,5-7,9,12,36 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).